



in which:

$X_1, X_2, X_3, X_4$ , which may be the same or different from one another, is selected from the group consisting of  $-\text{CONR}-$ ,  $-\text{NRCO}-$ ,  $-\text{OCO}-$ ,  $-\text{COO}-$ ,  $-\text{CH}_2\text{NR}-$  and  $-\text{NR-CH}_2-$ , where R is H or a  $\text{C}_{1-3}$  alkyl or benzyl;

f, g, h, m, which may be the same or different from one another, represent a number selected from the group consisting of 0, 1 and 2;

$R_1$  and  $R_2$ , which may be the same or different from one another, represent a  $-(\text{CH}_2)_r-$  Ar group, where  $r = 0, 1, 2$  and where Ar is an aromatic group selected from the group consisting of: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, said Ar group being possibly substituted with a maximum of two residues selected from the group consisting of  $\text{C}_{1-3}$  alkyl or halo-alkyl,  $\text{C}_{1-3}$  alkoxy,  $\text{C}_{2-4}$  amino-alkoxy, halogen, OH,  $\text{NH}_2$ , and  $\text{NR}_{13}\text{R}_{14}$  where  $R_{13}$  and  $R_{14}$ , which may be the same or different from one another, represent hydrogen or  $\text{C}_{1-3}$  alkyl; wherein  $R_3$  is selected from the group consisting of:

-hydrogen,

-linear or branched alkyl having the formula  $\text{C}_n\text{H}_{2n+1}$ , with  $n = 1-5$ , cyclo-alkyl or alkylcyclo-alkyl groups having the formula  $\text{C}_n\text{H}_{2n+1}$ , with  $n = 5-9$ ,

Sub C1  
cont.

~~-(CH<sub>2</sub>)<sub>r</sub>-Ar<sub>1</sub> group, where r = 0, 1, 2 and where Ar<sub>1</sub> is an aromatic group selected from the group consisting of: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzoimidazole, said Ar<sub>1</sub> group being possibly substituted with a maximum of two residues selected from the group consisting of C<sub>1-3</sub> alkyl or halo-alkyl, C<sub>1-3</sub> alkoxyl or aminoalkoxyl, halogen, OH, NH<sub>2</sub> and NR<sub>13</sub>R<sub>14</sub> where R<sub>13</sub> and R<sub>14</sub>, which may be the same or different from one another, represent hydrogen or C<sub>1-3</sub> alkyl;~~

wherein R<sub>4</sub> is selected from the group consisting of:

-hydrogen or C<sub>1-6</sub> alkyl,

-L-Q, where L is a chemical bond or a linear or branched C<sub>1-6</sub> alkyl residue and Q is selected from the group consisting of:

i) H, OH, OR<sub>9</sub>, NH<sub>2</sub>, NR<sub>9</sub>R<sub>10</sub>, guanidine, sulfate, phosphonate and phosphate

where R<sub>9</sub> and R<sub>10</sub>, which may be the same or different from one another,

represent a hydrogen C<sub>1-3</sub> alkyl group, C<sub>1-3</sub> hydroxyalkyl, C<sub>1-3</sub> dihydroxyalkyl, C<sub>1-3</sub>alkyl-CONHR<sub>12</sub>, C<sub>1-3</sub>alkyltetrazole, C<sub>1-3</sub>alkyl-COOH or wherein R<sub>9</sub>R<sub>10</sub> joined

together form with the N-atom a saturated 4-6 membered heterocycle possibly containing a further heteroatom selected from the group consisting of N, O and S and

wherein R<sub>12</sub> is a mono-, di-, tri-glycosidic group possibly protected with one or more C<sub>1-3</sub>-acyl groups or substituted with amino-groups or C<sub>1-3</sub> acylamino-

groups;

ii) COOH, tetrazole, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHCOOR<sub>8</sub>, CONHR<sub>8</sub>, NHCOR<sub>8</sub>, where R<sub>8</sub>

represents a linear or cyclic C<sub>1-6</sub> alkyl chain containing one or more polar groups

selected from the group consisting of: OH, NR<sub>15</sub>R<sub>16</sub>, COOH, CONHR<sub>12</sub>, PO<sub>3</sub>H and

SO<sub>3</sub>H, OR<sub>11</sub> and where R<sub>15</sub> and R<sub>16</sub>, which may be the same or different from one

another, represent a hydrogen or C<sub>1-3</sub> alkyl group, and where R<sub>11</sub> is a C<sub>1-3</sub> alkyl or C<sub>2-4</sub>

amino-alkyl chain, R<sub>12</sub> is a mono-, di-, tri-glycosidic group possibly

protected with one or more C<sub>1-3</sub>acyl groups or substituted with amino-groups or

C<sub>1-3</sub>acylamino-groups or R<sub>15</sub>R<sub>16</sub> joined together form with the N-atom a

saturated 4-6 membered heterocycle possibly substituted with C<sub>1-3</sub>alkyl-groups

or with saturated 4-6 membered heterocycle-groups containing at least an N-

atom;

iii) COOR<sub>17</sub>, CONHR<sub>12</sub>, OR<sub>12</sub> where R<sub>12</sub> is a mono-, di-, tri-glycoside group

Sub C17  
cont.

possibly protected with one or more  $C_{1-3}$  acyl groups or substituted with amine or  $C_{1-3}$  acylamine groups and  $R_{17}$  is a group  $R_{12}$  as above defined or a group  $C_{1-3}$  alkyl,  $C_{1-3}$  alkylphenyl, wherein the phenyl-group can be substituted with a group OH,  $NO_2$ ,  $NH_2$ ,  $CN$ ,  $CH_3$ , Cl, Br;  
 $R_5$ ,  $R_6$ ,  $R_7$ , which may be the same or different from one another, represent a hydrogen or  $C_{1-3}$  alkyl group; with the proviso that when  $R_1$  or  $R_2$  are benzyl or 4-hydroxybenzyl then  $R_3$  and  $R_4$  are isopropyl and an acceptable salt or enantiomer thereof.

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cont.

2. (Amended) Compound according to Claim 1, in which:

f, g, h, m, which may be the same or different from one another, may be 0 or 1;

$R_1$  and  $R_2$  which may be the same or different from one another, represent the side chain of a natural amino acid selected from the group consisting of tryptophan, phenylalanine, tyrosine and histidine, or the side chain of a non-natural amino acid selected from the group consisting of:

tryptophan and phenyl alanine, either mono- or di-substituted with residues selected from the group consisting of  $C_{1-3}$  alkyl or halo-alkyl,  $C_{1-3}$  alkoxy or amino-alkoxy, halogen, OH,  $NH_2$  and  $NR_{13}R_{14}$ , where  $R_{13}$  and  $R_{14}$ , which may be the same or different from one another, represent a hydrogen or  $C_{1-3}$  alkyl group;

$R_3$  is selected from the group consisting of:

- linear or branched alkyl having the formula  $C_nH_{2n+1}$  with  $n = 1-5$  (selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl and t-butyl) cycloalkyl or alkylcycloalkyl of formula  $C_nH_{2n-1}$  with  $n = 5-9$  (selected from the group consisting of cyclopentyl, cyclohexyl and methylcyclohexyl)

$-(CH_2)_r-Ar_1$ , where  $r = 1$  or  $2$  and where  $Ar_1$  is an aromatic group selected from the group consisting of:  $\alpha$ -naphthyl,  $\beta$ -naphthyl, phenyl, indole, said  $Ar_1$  group being possibly substituted with a maximum of two residues selected from the group consisting of:  $C_{1-3}$  alkyl,  $CF_3$ ,  $C_{1-3}$  alkoxy, Cl, F, OH and  $NH_2$ ;

$R_4$  represents an L-Q group where:

L is a chemical bond or  $CH_2$ , and

Q is selected from the group consisting of:

– OH, NH<sub>2</sub>, NR<sub>9</sub>R<sub>10</sub>, OR<sub>11</sub>, and where R<sub>9</sub> and R<sub>10</sub>, which may be the same or different from one another, represent a hydrogen or C<sub>1-3</sub> alkyl group, C<sub>1-3</sub>hydroxy alkyl, C<sub>1-3</sub>dihydroxyalkyl, C<sub>1-3</sub>alkyl-CONHR<sub>12</sub> (wherein R<sub>12</sub> is a monoglycosidic group derived from D or L pentoses or hexoses (selected from the group consisting of ribose, arabinose, glucose, galactose, fructose, glucosamine and galactosamine and their N-acetylated derivatives)), C<sub>1-3</sub>alkyltetrazole, C<sub>1-3</sub>alkyl-COOH or wherein R<sub>9</sub>R<sub>10</sub> are joined together to form with the N atom a morpholine or a piperidine ring and where R<sub>11</sub> is a C<sub>1-3</sub> alkyl chain, or a C<sub>2-4</sub> amino-alkyl chain; NHCOR<sub>8</sub> wherein R<sub>8</sub> is a cyclohexane containing from 2 to 4 OH groups, C<sub>1-6</sub> alkyl chain containing a polar group (chosen in the group consisting of NH<sub>2</sub>, COOH, CONHR<sub>12</sub>, (wherein R<sub>12</sub> is as hereabove defined) or [1,4']bipiperidine) – COOH, COOR<sub>17</sub> or CONHR<sub>12</sub>, wherein R<sub>12</sub> is as hereabove defined and R<sub>17</sub> is as R<sub>12</sub> or a group 4-nitrobenzyl.  
– R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> are H,  
in which the carbon atom that carries the substituents R<sub>3</sub> and R<sub>7</sub> has configuration R.

3. (amended twice) A compound according to Claim 2 selected from:

- (a) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}
- (b) Cyclo{-Suc-Trp-Phe-[(S)-NH-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}
- (c) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>11</sub>)-CH<sub>2</sub>-NH]}
- (d) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>(4-OCH<sub>3</sub>))-CH<sub>2</sub>-NH]}
- (e) Cyclo{-Suc-Trp(5F)-Phe-[(R)-NH-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}
- (f) Cyclo{-Suc-Trp(Me)-Phe-[(R)-NH-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}
- (g) Cyclo{-Suc-Phe(3,4-Cl)-Phe-[(R)-NH-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}
- (h) Cyclo{-Suc-Trp-Phe(3,4-Cl)-[(R)-NH-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}
- (i) Cyclo{-Suc-Trp-Tyr-[(R)-NH-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}
- (j) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>-3,4-diCl)-CH<sub>2</sub>-NH]}
- (k) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-4-OH)-CH<sub>2</sub>-NH]}
- (l) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}

- Sub C<sup>2</sup>  
cont.
- (m) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-2-naphthyl)-CH<sub>2</sub>-NH]}
- (n) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-indol-3-yl)-CH<sub>2</sub>-NH]}
- (o) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-5-F-indol-3-yl)-CH<sub>2</sub>-NH]}
- (p) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>-3-F)-CH<sub>2</sub>-NH]}
- (q) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>-3,4-diF-CH<sub>2</sub>-NH)-]}
- (r) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>-4-CF<sub>3</sub>-CH<sub>2</sub>-NH)-]}
- (s) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH<sub>2</sub>-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)-NH]}
- (t) Cyclo{-Suc-Trp-Phe-[(S)-NH-CH<sub>2</sub>-CH(CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)-NH]}
- (u) Cyclo{-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-(CH<sub>2</sub>)<sub>3</sub>CO-}
- (v) Cyclo{-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-N(CH<sub>3</sub>)-(CH<sub>2</sub>)<sub>3</sub>CO-}
- (w) Cyclo{-Suc[1(S)-NH<sub>2</sub>]-Trp-Phe-[(R)NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]-}
- (x) Cyclo{-Suc[1(R)-NH<sub>2</sub>]-Trp-Phe-[(R)NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]-}
- (y) Cyclo{-Suc[2(S)-NH<sub>2</sub>]-Trp-Phe-[(R)NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]-}
- (z) Cyclo{-Suc[2(R)-NH<sub>2</sub>]-Trp-Phe-[(R)NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]-}
- (aa) Cyclo{-Suc[1(S)-NH(CH<sub>3</sub>)]-Trp-Phe-[(R)NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]-}
- (ab) Cyclo{-Suc[1-COO(CH<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>-4-NO<sub>2</sub>)]-Trp-Phe-[(R)NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]-}
- (ac) Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}  
[Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}]
- (ad) Cyclo{-Suc(1-OH)-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}
- (ae) Cyclo{-Suc(2-COOH)-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}
- (af) Cyclo{-Suc(2-OH)-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]}
- (ag) Cyclo{-Suc[1(S)-(2H-tetrazolyl-5-ylmethyl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-} trifluoro-acetic acid
- (ah) Cyclo{-Suc[1(S)-(morpholin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-} trifluoroacetic acid
- (ai) Cyclo{-Suc[1(S)-N(CH<sub>3</sub>)<sub>2</sub>]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-} trifluoroacetic acid
- (aj) Cyclo{-Suc[1(S)-(piperidin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-} trifluoroacetic acid
- (ak) Cyclo{-Suc[1(S)-(N(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>)]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-} trifluoroacetic acid

- Sub C2  
Cont.
- BK  
Complete
- (al) Cyclo{-Suc[1(S)-(N(CH<sub>2</sub>CH(OH)CH<sub>2</sub>OH)]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-} trifluoroacetic acid
- (am) Cyclo{-Suc[1(S)-(3-carboxypropanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-}.
- (an) Cyclo{-Suc[1(S)-[3-N'-β-D-glucopiranos-1-yl]-carboxamidopropanoyl]amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-}
- (ao) Cyclo{-Suc[1(S)-[(carboxymethyl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-} trifluoroacetic acid
- (ap) Cyclo{-Suc[1(S)-[N'-β-D-glucopiranos-1-yl]-carboxyamideomethyl]amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-} trifluoroacetic acid
- (aq) Cyclo{-Suc[1(S)-(chiny)amine]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-}
- (ar) Cyclo{-Suc[1(S)-(4-aminobutanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-} trifluoroacetic acid
- (as) Cyclo{-Suc[1(S)-[1,4']bipiperidin-1-yl]acetamido]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-} trifluoroacetic acid
- (at) Cyclo{-Suc[1-N-(β-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-}
- (au) Cyclo{-Suc[1(S)-[N'-(2-N-acetyl-β-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>-NH]-}.

B7 Sub C3

5. (Amended) A composition comprising a compound of general formula (I) according to Claim 1 in combination with a suitable carrier or excipient..

6. (Amended) A composition according to Claim 5, adapted for use as a tachykinin antagonist.

7. (Amended) A composition according to Claim 6, adapted for use as an antagonist of the human neurokinin-2 (herein NK-2) receptor.

QPS

8. (Amended) A composition according to Claim 7, adapted for use in the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary

*B7*  
*conclude*

irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics.

*B8* *Sub C5*

12. (Amended) A method of antagonizing an NK-2 receptor in a mammal afflicted with asthma comprising contacting an NK-2 receptor in said mammal with a compound according to Claim 1 for a time and under conditions effective to antagonize an NK-2.

13. (Amended) A method of antagonizing an NK-2 receptor in a mammal afflicted with an anxiety disorder comprising contacting an NK-2 receptor with a compound according to Claim 1 for a time and under conditions effective to antagonize an NK-2 receptor.

*B9* *Sub C6*

14. (Amended) A method for the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and if the ureter during cystitis, and kidney infections and colics, in which quantities of between 0.02 and 10 mg/kg of body weight of active principle consisting [of products] of formula (I), according to Claim 1, are administered to the patient for a time and under conditions effective to antagonize an NK-2 receptor.

*B10*

16. (New) A method of antagonizing a neurokinin-2 (NK-2) receptor comprising contacting an NK-2 receptor with a compound according to claim 1 for a time and under conditions effective to antagonize said NK-2 receptor.

17. (New) A method of antagonizing a neurokinin-2 (NK-2) receptor comprising administering to a mammal in need thereof a compound according to claim 1 for a time and under conditions effective to antagonize the NK-2 receptor.

18. (New) The method according to claim 17 wherein said mammal is afflicted with a disorder selected from the group consisting of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics.